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Research paper

Pharmacoscintigraphic evaluation of lipid dry powder budesonide formulations for inhalation

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Abstract

Lung deposition of new formulations of budesonide, using solid lipid microparticles (SLmP) as a pharmaceutically acceptable filler and carrier for inhalation aerosols, and administered from a dry powder inhaler (Cyclohaler®), were compared with that from Pulmicort® Turbuhaler®. Six healthy volunteers took part in a three-way randomized cross-over study, and inhaled a nominal dose of 400 μg budesonide, labelled with ^{99m}Tc, on each study day. Lung deposition was determined by gamma scintigraphy and by a pharmacokinetic method. The percentage of dose (SD) in the whole lung was 49.9 (3.7)% for the lipidic matricial form (M) and 62.8 (4.9)% for the lipidic physical blend formulation (PB). These results corresponded well with the in vitro fine particle assessment. In comparison with data recorded in literature for in vivo deposition obtained with Pulmicort® Turbuhaler®, it was estimated that lung deposition was 1.5 and 2.0 times higher for the M and PB formulations, respectively. Furthermore, the relative drug availability obtained from the pharmacokinetic evaluation, expressed as the percentage of pulmonary absorption of the comparator product, was 154% and 220% for M and PB, respectively.

The results of the present study indicate that pulmonary administration using SLmP gives a prominent and significant increase in budesonide lung deposition.

Keywords: Solid lipid particles; Dry powder inhaler; Gamma scintigraphy; Total and regional lung deposition; Pharmacokinetics

1. Introduction

Asthma is a chronic inflammatory disease of the airways characterized by recurrent breathing problems that are usually triggered by allergens, infection or other factors. It is treated with a variety of drugs including β_2-agonist, anti-cholinergic and anti-inflammatory compounds (both steroidal and non-steroidal). These active substances are commonly delivered by the inhaled route using a variety of inhalation devices, including nebulizers, pressurised metered dose inhalers and dry powder inhalers [1].

Inhalation of the drug enables a rapid and predictable onset of action and induces fewer side effects than does administration by other routes [2]. However, these advantages are often associated with limited lung deposition and short duration action because of the protective mechanisms of the respiratory tract [3,4].

In a previous work, we developed budesonide dry powder formulations for inhalation using solid lipid microparticles (SLmP) as pharmaceutically acceptable filler and/or

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carrier in order to overcome the limitations related to pulmonary administration of the drug [5].

The SLmP were evaluated for their physical characteristics and in vitro deposition measurements were performed using the Multi-stage Liquid Impinger (MsLI) and compared to those using Pulmicort® Turbuhaler® DPI (AstraZeneca), a marketed form of budesonide. The SLmP appeared to be spherical low-density material characterized by a smooth surface. The mass median diameter ($D(0,5)$), and the volume mean diameter ($D(4,3)$) were tiny and ranged from 1.7 to 3.1 μm and from 2.0 to 3.9 μm, respectively. The SLmP formulations, delivered by the Cyclohaler® inhaler, were found to emit a fine particle dose (FPD) of 93–113 μg, which was considered to be very promising compared to the FPD value (68 μg) of Pulmicort® Turbuhaler® [5].

In order to confirm these encouraging results, two of the SLmP formulations were selected on the basis of their aerodynamic behaviour and FPD values and compared to Pulmicort® Turbuhaler® by performing a combined in vivo scintigraphic and pharmacokinetic evaluation of inhaled budesonide after a single inhalation in six healthy volunteers. Gamma scintigraphic imaging provides direct information on the amount and the site of drug deposition in the lung after inhalation. Moreover, the pharmacokinetic evaluation also gives valuable information on the local bioavailability of drugs as higher drug deposition and deeper drug penetration into the lung correspond to higher drug plasma concentrations owing to the rapid elimination of the drug from the site of deposition by absorption.

2. Materials and methods

2.1. Inhaler devices and dry powder formulations

Two devices were used: Cyclohaler® (Novartis, Switzerland), a passive breath-actuated, single-dose dry powder inhaler loaded with size #3 HPMC capsules containing 200 μg budesonide for the SLmP formulations; and Pulmicort® Turbuhaler® (AstraZeneca, Sweden), a multidose dry powder inhaler also available with 200 μg budesonide per puff.

The first SLmP formulation selected was a physical blend formulation (PB). It consisted of a physical blend of 2% (by weight) micronized budesonide (CHEMO IBERICA, Spain) and 98% of the lipid carrier (with a weight ratio cholesterol (MERCK, Germany):Phospholipon® 90H (Nattermann Phospholipid, Germany) of 90:10). Size #3 HPMC capsules (CAPSUGEL, France) were loaded with 10 mg of this powder (200 μg budesonide).

The second SLmP formulation was a matricial formulation (M), containing 2% (by weight) micronized budesonide, 8% Phospholipon® 90H and 90% cholesterol. Size #3 HPMC capsules were loaded with 10 mg of this powder.

The lipid components were obtained by spray-drying a lipidic solution through a laboratory-scale spray-dryer according to previously described methods [5].

The third formulation was the comparator product, Pulmicort® Turbuhaler®.

2.2. The radionuclide imaging method

It was recognized in the late 1970s that the powerful images and data obtained in nuclear medicine could play a significant role in the assessment of drug delivery, initially in the gastrointestinal tract. Radionuclide imaging has subsequently been used to assess drug delivery by a variety of routes, including the lungs [6,7].

One of the most commonly used techniques, known as gamma scintigraphy, involves taking two-dimensional "planar" views of radionuclide distributions with a single-headed or dual-headed gamma camera. Typical radiolabelling methods involve adsorbing ^{99m}Tc as sodium pertechnetate onto the surface of drugs particles in a dry powder inhaler [6]. This gamma-ray emitting element has an ideal energy (140 keV) for use with a gamma camera, its short half-life of 6 h coupled with a very clean radiation emission profile results in very low radiation doses [8].

2.3. The radiolabelling method

The method used was based upon a technique developed and described elsewhere, which is based on the adsorption of the radiolabel onto the surface of the dry particles [9].

In brief, for the physical blend formulation (PB), the drug was labelled by adding it to water containing ^{99m}Tc pertechnetate. The water was removed by freeze-drying, leaving the radiolabel attached to the drug particles, and the radiolabelled active drug was passed through a 315 μm sieve before being blended with the lipidic carrier.

For technical reasons, the matricial formulation (M) was radiolabelled by adding the finished product, rather than only the active substance, to water containing ^{99m}Tc pertechnetate.

On the other hand, a Pulmicort Turbuhaler® device was emptied and the spheres of budesonide were mixed with ^{99m}Tc in water until they were completely wet. After freeze-drying, the device was re-filled with the radiolabelled powder and primed by firing 10 shots to waste [10].

2.4. Validation of the radiolabelling method

In order to assess whether the radiolabelling process had any effect on the particle size distribution of the drug and also to determine the degree to which the radiolabel distribution would reflect the distribution of the drug substance, validation experiments were carried out prior to starting the clinical part of the investigation. For each formulation, the FPD and the particle size distribution of the unlabelled drug were determined then compared against those of the labelled drug and of the radiolabel ($n = 3$). The measurements were made with a Multistage Liquid Impinger

(MsLI, Copley instruments, UK) operating at an air flow rate corresponding to a pressure drop of 4 kPa across each inhaler (Eur. Pharm. 5th ed.). The test was carried out at 100 L/min for 2.4 s and at 60 L/min for 4 s for the Cyclohaler® and the Pulmicort® Turbuhaler®, respectively. Drug and radiolabel content at each stage of the MsLI were determined by a validated analytical HPLC method [5] and by gamma counting (using a Cobra gamma counter, Packard Bioscience, UK), respectively. The FPD was defined as the fraction of the drug or the radiolabel corresponding (by interpolation) to particles having an aerodynamic diameter inferior to 5 μm and was calculated as a percentage of the nominal dose, i.e. the fine particle fraction (FPF). The FPD is considered to be directly proportional to the amount of drug able to reach the pulmonary tract in vivo: consequently, the higher the value of the FPD (or FPF), the deeper the lung deposition is estimated to be.

It should be noted that since the radiolabel is adsorbed onto the surface of the drug particles, its particle size distribution (as determined by a gamma counting technique) corresponds to that of the drug particles.

2.5. Study design

The study design was an open single-dose, three-treatment, three-period cross-over study with wash-out period of at least 6 days between the three phases of the study. Two subjects were randomly assigned to each of the three possible dosing sequences.

All volunteers received the drug treatment as two capsules of 200 μg budesonide (PB and M formulations) or two puffs of Pulmicort® Turbuhaler® 200 μg on each occasion.

The amount of ^{99m}Tc was adjusted so that the maximum amount of radioactivity inhaled by the subjects on any occasion did not exceed 10 MBq of ^{99m}Tc. The maximum effective dose in this study was less than that received from a single abdominal X-ray and therefore the risk to the subject from radiation was considered to be very small. Additionally, 1 g/5 mL of sodium perchlorate (Erasme Hospital, Belgium) was administered about 30 min prior to inhalation to prevent thyroid uptake of the radiolabel element. Furthermore, a total of 50 g of activated charcoal (Carbomix, Norit, The Netherlands) was given orally before and over the 10 min after each administration of drug treatment to prevent gastrointestinal absorption (GI) of budesonide [11,12].

Prior to the administration of the radiolabelled aerosol, subjects practised the breathing manoeuvre to be used with the aid of an empty device. After holding their breath for 5 s, they exhaled through a filter in order to trap any aerosol particles in the expired air. Once the investigator was satisfied that the subject could perform the correct breathing technique reproducibly, the practice device was replaced with a device containing the radiolabelled formulation.

2.6. Volunteers

Six healthy male volunteers were included in the study on the basis of inclusion and exclusion criteria and medical examination. All had lung function values within the normal limits, their mean forced expiratory volume in one second (FEV_1) was 102% (87–119%) and vital capacity 92% (81–103%) of predicted normal values [13]. They were preferably non-smokers and were free from clinically significant pathology.

Before starting the study, the nature of the clinical trial was explained and written consent was obtained from all volunteers. The study was conducted at the Erasme Hospital (Brussels, Belgium), in accordance with the principles stated in the Declaration of Helsinki, and approval was obtained from the Ethics Committee of Erasme Hospital (Ref.: P2004/202) and the Belgian Minister of Social Affairs and Public Health (Ref.: EudraCT No. 2004-004658-14).

2.7. Gamma scintigraphy

Immediately following the administration of the radiolabelled aerosol, scintigraphic images of the chest (posterior and anterior) and lateral oropharynx were recorded (DHD-SMV, Sopha Medical, France). The empty device and capsule (Cyclohaler®), mouthpiece (Pulmicort® Turbuhaler® DPI) and exhalation filter were also counted [9].

The edges of the lungs were delineated using a ^{99m}Tc transmission scan and the lungs were subdivided into central, intermediate and peripheral regions of interest, corresponding approximately to large, medium and small airways [14–17]. Regions of interest were also drawn around the oropharynx, oesophagus and stomach (including any activity in the small intestine). The counts obtained within these regions were corrected for background radioactivity, radioactive decay, and for tissue attenuation [18]. In the regions where both anterior and posterior images were recorded, the geometric mean of counts in both images was calculated prior to correction for tissue attenuation.

Determination of the percentage of the dose deposited in the oropharynx included activity adhering to the mouth and oropharynx together with any swallowed activity detected in the oesophagus, stomach and intestine. Any activity detected on the mouthpiece or the exhalation filter was deemed to be due to direct transfer from the mouth. This activity was analysed with a separate region of interest and the counts added to those for the oropharynx.

The counts in each named area were expressed as a percentage of the metered dose which was determined from the sum of the total body counts and those from the Pulmicort® Turbuhaler® mouthpiece or the Cyclohaler® inhaler device and capsules, and the exhalation filter. The percentage lung deposition data were multiplied by the nominal budesonide dose in order to provide data on the mass of budesonide deposited in the lungs. Furthermore, the regional lung deposition patterns were assessed by using

the most commonly defined penetration index. This index was obtained from the ratio of peripheral lung zone deposition to central lung zone deposition (P:C ratio) [15,16].

2.8. Lung function tests

Forced expiratory volume in one second (FEV1) was recorded, using a portable Spirometer (Alpha III, Vitalograph Ltd, UK), prior to and 30 min after inhalation in order to check whether the inhaled formulations had led to any significant bronchoconstriction.

2.9. Pharmacokinetics

Venous blood samples (7 mL) were collected at pre-dose and at 10, 20, 30, 40, 50 min, 1 h, 1 h:30, 2 h, 2 h:30, 3 h, 3 h:30, 4 h, 4 h:30, 5 h and 6 h post-dose in order to quantify plasma levels of budesonide. After centrifugation, the plasma samples were decanted and divided into two approximately equal portions of not less than 2.00 mL per tube (aliquot) and rapidly stored at −80 °C, in an upright position. The concentration of the active drug was measured using a validated LC/MS–MS method (high-performance liquid chromatography) (HP 1100 series, Agilent Technologies, Belgium) and an API3000 triple quadrupole mass spectrometer (Applied Biosystems/MDS Sciex, Concord, Canada). Maximal plasma concentration (C_{max}) and time to maximal plasma concentration (T_{max}) were taken directly from the plasma concentration vs. time curve. Area under the curve (AUC) was calculated by the linear trapezoidal rule from measured data points from time of administration until the time of the last quantifiable concentration.

2.10. Statistical analysis

The repeated-measures ANOVA test was used to validate the radiolabelling method and to compare the pharmacokinetic data obtained with the three formulations. The paired *t*-test was used to compare the lung deposition pattern between PB and M products. For all tests, the significance level was set at $p = 0.05$.

3. Results

3.1. Validation of the radiolabelling method

The particle size distributions for the PB formulation, as determined in the MsLI, are given in Fig. 1. The mean (SD) FPF values obtained for the drug before labelling (57.6 (2.9)%) and after labelling (55.2 (1.8)%) and for the radiolabel (59.3 (2.5)%) were not significantly different ($p > 0.05$). The data for the M formulation are shown in Fig. 2. There was also a good match between the mean (SD) FPF of the drug before labelling (46.8 (0.7)%) and after labelling (44.3 (0.7)%) and for the radiolabel (47.6 (3.1)%) ($p > 0.05$). Indeed, for both lipid dry powder formulations a homogeneous drug and radiolabel fractionation between the different stages of the impinger were obtained (Figs. 1 and 2).

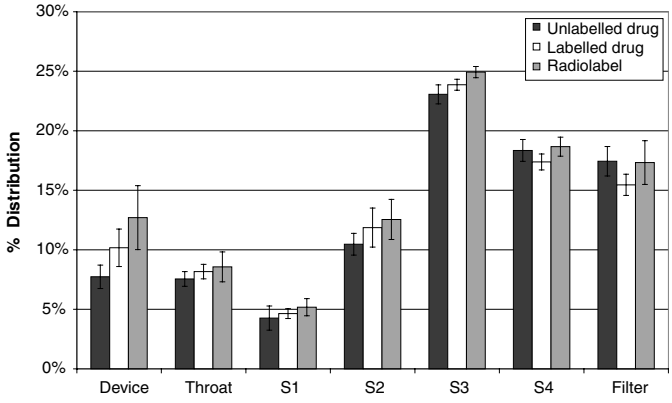

Fig. 1. Percentage of unlabelled budesonide, labelled budesonide, and radiolabel for the PB formulation in the different stages of MsLI ($n = 3$).

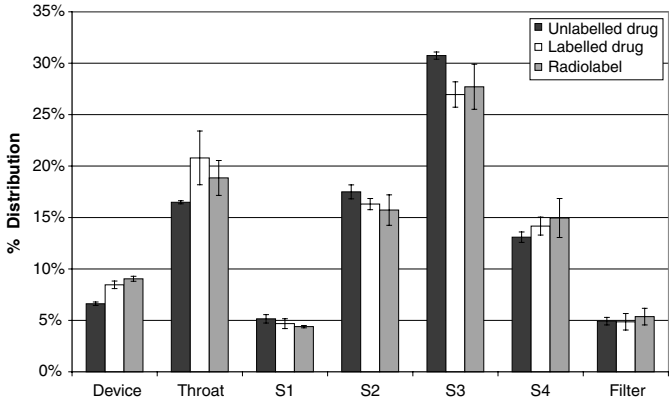

Fig. 2. Percentage of unlabelled budesonide, labelled budesonide, and radiolabel for the M formulation in the different stages of MsLI ($n = 3$).

For the lipid dry powder formulations, these data demonstrated that the radiolabelling process did not significantly alter the particle size distribution and was considered suitable for use. However, this was not the case for the Pulmicort® Turbuhaler® radiolabelling method (data not shown). We were not able to re-form, after the freeze-drying and the sieving stages, the typical spheres of budesonide enclosed in the Turbuhaler device. Unfortunately, the detail of the method used to wet the spherical agglomerates of budesonide powder with ^{99m}Tc solution is not fully described in the literature. Therefore, this formulation was used without being radiolabelled during the clinical study and thus no experimental scintigraphic results were obtained for the comparator. The mean (SD) FPF for the drug before labelling was 34.1 (2.3)%.

3.2. Scintigraphic results

The scintigraphic images showing deposition patterns for each of the SLmP formulations are illustrated in Fig. 3. The fractionation of the delivered dose between

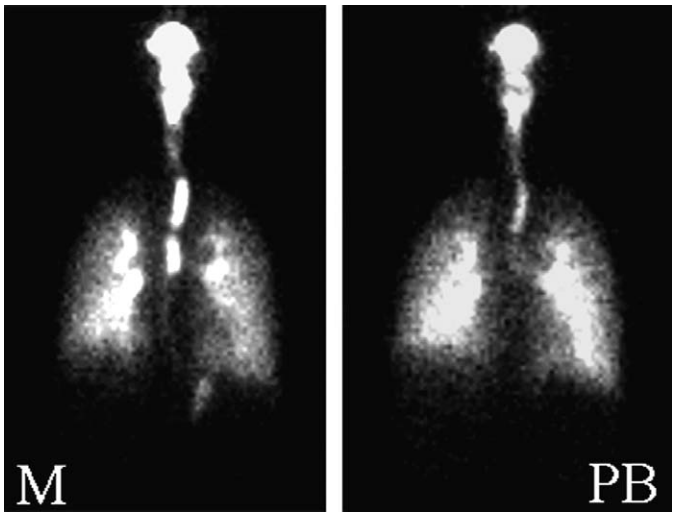

Fig. 3. Scintigraphic images obtained using Cyclohaler® loaded with M (left inside) and PB (right inside) formulations.

the whole lungs, oropharynx, the device and the exhalation filter is shown in Table 1. The mean (SD) lung deposition for the PB formulation was 62.8 (4.9)%, which was significantly greater ($p < 0.05$) than the one for the M formulation (49.9 (3.7)%). These results corresponded to 251.2 (19.8) and 199.6 (15) μg budesonide deposited in the lung, assuming a total delivered dose of 400 μg over two shots via the Cyclohaler® loaded with PB and M products, respectively. Oropharyngeal deposition for the matricial form was significantly higher than that for the physical blend formulation ($p < 0.05$). Moreover, there was a significant difference concerning the device retention ($p < 0.05$) although the numerical difference between the two formulations was small. The exhaled fraction was found to be less than 0.2% for both products and was assumed to be negligible.

The regional lung deposition patterns are given in Table 2. Careful examination of Table 2 shows that the increase in the total lung deposition for PB as compared to M was reflected in approximately equal, and statistically significant ($p < 0.05$), increases in central, intermediate and peripheral depositions. Indeed, the P:C ratio did not vary

Table 1
Mean (SD) fractionation of the dose between lungs, oropharynx, device and exhaled air filter, for the PB and M formulations in six healthy volunteers

Deposition area	Formulation		*P*-value
	PB	M	
Lungs	62.8 (4.9)	49.9 (3.7)	0.003**
Oropharynx	26.8 (3.8)	38.0 (3.1)	0.006**
Device	10.4 (2.6)	12.1 (2.2)	0.04*
Exhaled air	0.13 (0.08)	0.11 (0.07)	0.297 (NS)

Data are expressed as percentage.
NS: not significantly different, $p > 0.05$.
* $p < 0.05$.
** $p < 0.01$.

Table 2
Regional lung deposition: mean (SD) percentage deposition in peripheral, intermediate and central lung zones, and mean (SD) peripheral zone/central zone deposition ratio (P:C ratio)

Deposition area	Formulation		*P*-value
	PB	M	
Peripheral zone	22.0 (3.9)	17.4 (2.6)	<0.001***
Intermediate zone	22.1 (2.4)	16.9 (2.0)	<0.001***
Central zone	18.6 (2.6)	15.6 (2.3)	<0.001***
P:C ratio	1.2 (0.4)	1.1 (0.3)	0.207 (NS)

Data are expressed as percentage.
NS: not significantly different, $p > 0.05$.
*** $p < 0.001$.

significantly between PB (1.2 (0.4)) and M (1.1 (0.3)), ($p > 0.05$), and it indicated that more of the dose was deposited in medium and small-diameter airways and alveoli than in primarily large-diameter airways. Thus, in accordance with the previously published in vitro results [5], the scintigraphic results clearly show a significantly deeper and greater drug penetration for the PB formulation in comparison with the M formulation.

As indicated before, unfortunately we were not able to assess the lung deposition of the comparator via a scintigraphy technique. However, as a benchmark product, Pulmicort® Turbuhaler® has been widely studied and evaluated in numerous different studies. For example, Hirst et al. [19] showed in a scintigraphy study that the inhalation of Pulmicort® Turbuhaler® at an inspiratory rate of 30 and 60 L/min gave a mean (SD) whole lung deposition of 22.7 (5.6)% and 29.8 (6.9)%, respectively, while the results of Thorsson et al. [12] indicated a budesonide lung deposition from the Turbuhaler DPI of 32%. These results correspond well with the in vitro fine particle assessment, in which the FPD of budesonide via the Turbuhaler was found to be 34.1 (2.3)% which is significantly lower than the SLmP results.

3.3. Lung function tests

The FEV_1 values, measured prior to and 30 min after dosing, were similar on each study day (data not shown). It indicated that the inhalation of 400 μg budesonide with or without solid lipid particles (Pulmicort®, PB and M formulations) did not have any significant effects on lung function. Furthermore, no major or minor complications were observed during the clinical trial and there was no evidence of bronchoconstriction, suggesting good tolerance of these products.

3.4. Pharmacokinetic data

It should be noted that a highly sensitive and selective LC/MS–MS method has been developed for the separate quantification of A and B epimers of budesonide in human plasma. The content of the epimer A (second peak) is 40.0–51.0% of the sum of the areas of the two epimer peaks (Eur.

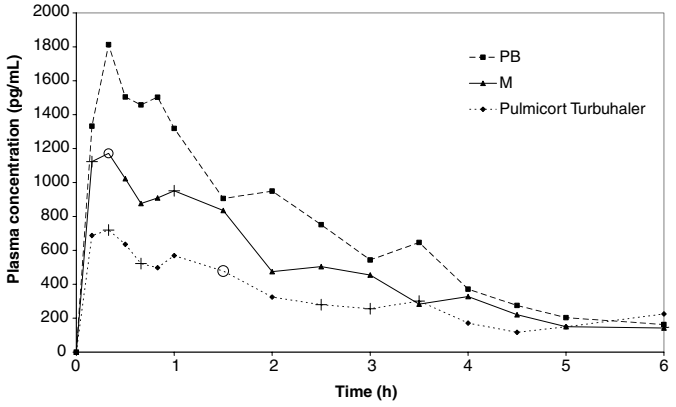

Fig. 4. Mean plasma concentrations of budesonide epimer B plotted vs. time for the three formulations evaluated. +, Mean of five individual data points. ○, Mean of four individual data points.

Table 3
Mean (SD) pharmacokinetic parameters (for budesonide epimer B)

	Formulation			*P*-value
	PB	M	Pulmicort	
AUC (pg/mL h)	4170 (400)	2905 (730)	1890 (275)	<0.001***
C_{max} (pg/mL)	2050 (500)	1640 (484)	812 (139)	<0.001***
T_{max} (h)	0.47 (0.29)	1.00 (0.88)	0.36 (0.27)	0.136 (NS)

NS: not significantly different, $p > 0.05$.
*** $p < 0.001$.

Pharm. 5th ed.), and its overall plasma concentration–time profile is similar to that of the epimer B.

The examination of Fig. 4, representing the plasma concentration–time profile of the epimer B, showed a rapid plasma concentration peak for SLmP formulation as well as for the comparator product (T_{max} of 0.4–1.0 h), followed by a progressive decrease in budesonide plasma concentrations over 6 h. Unfortunately, no delay in the drug release can be observed from the pharmacokinetic results as was expected from the lipid matrix formulation [5].

As can be observed from the examination of the pharmacokinetic data shown in Table 3, the C_{max} and AUC values were found to be significantly higher for PB and M formulations than for Pulmicort® Turbuhaler® ($p < 0.05$). For example, the C_{max} values were found to be 2050, 1640 and 812 pg/mL for the PB, M and Pulmicort®, respectively. The $AUC_{PB/Pul}$, and $AUC_{M/Pul}$ quotients were estimated to be 2.20 and 1.54, respectively. However, as the inter-subject variability was relatively high, the clinical trial should be carried out on a higher number of volunteers in order to confirm these results.

4. Discussion

In this study, two kinds of formulation using solid lipid microparticles as drug delivery agents for inhalation aerosols were compared to Pulmicort® Turbuhaler® by a pharmacoscintigraphy method. This method combines the acquisition of radionuclide imaging data, which provides direct information on the local bioavailability, and pharmacokinetic data, which gives information on the systemic bioavailability, more specifically in this case on the elimination of drug from lung by absorption.

The in vitro validation of the radiolabelling procedure showed that the match between the radiolabelled and unlabelled active drug was within acceptable limits except for the comparator product. The latter was therefore not radiolabelled and the in vivo gamma scintigraphy permitted only the assessment of drug delivered by the Cyclohaler®. This technique indicated that 62.8% of the metered dose was deposited in the lungs for the PB formulation, which was found to be 1.26 times higher than the 49.9% total lung deposition of the M formulation. These results therefore corresponded well with the in vitro fine particle assessment, in which the FPD of budesonide from PB was 1.23 times higher than that from M. The difference between the aerodynamic behaviour and the deposited dose values of matrix and physical blend formulations could be explained by the fact that, for the M formulations, budesonide is homogeneously entrapped in the matrix and cannot separate from the lipidic excipients during inhalation. However, for the PB formulations, the drug particles are physically separate from the lipid carrier particles and so penetrate deeper in the lung [5] during inhalation. This is because the air flow energy generated during inhalation can promote the dispersion of budesonide particles owing to the presence of loose drug–carrier interactions and differences between particle sizes and densities.

The quantification of plasma levels of budesonide (corresponding mainly to the level of pulmonary absorption from the concomitant oral administration of activated charcoal, which prevents the GI absorption of drug) showed significantly higher C_{max} and AUC values for PB and M than for Pulmicort®. Therefore, the use of the Cyclohaler® loaded with such formulations yields plasma levels 2.20 and 1.54 times higher for PB and M, respectively, than for Pulmicort®. This was roughly in compliance with proportional differences between these products observed from the in vitro fine particle dose evaluations (FPF_{PB} 57.6% > FPF_{M} 46.8% > $FPF_{Pulmicort}$ 34.1%) and the in vivo scintigraphic deposition, considering the deposition results indicated in the literature for the Pulmicort® Turbuhaler® (deposition of 62.8% for PB, 49.9% for M and 29.8% for the comparator according to Hirst et al. [19]).

As indicated before, the pharmacokinetic evaluation gives indirect but very valuable information on the local bioavailability of drug as higher drug deposition and deeper drug penetration in the lung correspond to higher drug plasma concentrations owing to the rapid elimination of drugs from the site of deposition by absorption. Such an evaluation, in accordance with the in vitro deposition results and the in vivo scintigraphic deposition, confirms the superiority of dry lipid formulation in terms of drug deposition in comparison with conventional DPI formulations.

5. Conclusion

Even if we did not highlight any delayed effect or controlled-release properties, especially from the lipidic matricial form, the results of the present study suggest, from the increase in the deposition of budesonide in the pulmonary tract, that administration of solid lipid microparticles as carrier or filler agent may be useful in order to overcome some limitations related to the delivery of drugs by inhalation.

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